REMARKS/ARGUMENTS

Claims 39, 40 and 46-51 are active. Claims 1-38 were cancelled. Claim 39 has been revised and simplified by removing intended use limitations pertaining to detection of diabetes and by reference to particular SEQ ID NOs. Support for the identification of autoantibodies to ZnT-8 is found on page 20, lines 5-14 and in original claims 28 and 29. No new matter has been added. Favorable consideration of this Amendment and allowance of this application is respectfully requested.

Interview Summary

The Applicants thank Examiner Ewoldt for the courteous and helpful interview of January 21, 2010. The disclosure was reviewed for descriptive support for claims directed to detecting autoantibodies to ZnT-8 per se as well as for methods of detecting Type I diabetes by measuring autoantibodies to ZnT-8. The Examiner urged that Type I diabetes was mediated by cellular mechanisms, e.g., by T cells, and not by autoantibodies, and consequently detection of antibodies to beta cell antigens would not necessarily correlate with Type I diabetes. The Examiner also asked whether detection of autoantibodies to ZnT-8 would be useful, especially if ZnT-8 was not beta cell specific, for example, would the detection of autoantibodies to ubiquitous MHC Class I antigens also present on beta cells be useful? The Examiner also requested an explanation of the differences between Fig. 2 as originally submitted and the cleaner copy of Fig. 2 recently submitted in response to a drawing objection.

Figure 2

Replacement Figure 2 presents the same information as original Figure 2 except that the relatively high background in the original figure has been reduced to provide a better

figure. The new figure is not a small portion of the original figure. It is the same size, just cleaner. Figure 2 does not reproduce a microtiter plate impression, but rather an RT-PCR analysis of the mRNA encoding Zn-T8 protein, see page 30, lines 8-16 and Example 3 in the specification.

Objection--Specification

The specification was objected to as containing executable hyperlinks. This objection is moot in view of the inactivation of the hypertext.

Rejection—35 U.S.C. §112, first paragraph

Claims 39, 40, 46-51 and 55 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement as to "how to use" the invention without undue experimentation.

Initially, to provide a basis for discussion of the enablement issues, the Applicants point out descriptive support for the methods as now claimed. Page 20, lines 9-14 of the specification describe "use of the protein or of the protein fragment as defined above, for. . .the search for autoantibodies directed against the protein according to the invention". That is, the ZnT-8 protein and its fragments, see page 19, lines 26-34 and by original claims 24 and 25. Original claims 28 and 29 also disclose use of ZnT-8 "for detecting the presence of autoantibodies". The specification, section bridging pages 5-6, discloses that ZnT-8 is "expressed specifically in the islet of Langerhans, and more particularly in the insulin-secreting cell or beta cell". Page 6, lines 24-28 also discloses that ZnT-8 is a "specific and reliable marker for the beta cell of the pancreatic islets of Langerhans". Example 2 starting on page 31 of the specification shows that ZnT-8 mRNA is "expressed only in the pancreatic cells" and not in cells from 23 other tissue types analyzed, see page 32, lines 15-21 and Fig.

1a. Actin mRNA was expressed in all cell types, Fig. 1b. Methods of detecting autoantibodies that bind to a specific antigen were well-known as of the filing date and thus this section describes and enables a method for detecting autoantibodies to ZnT-8. Clearly, the inventors have shown that ZnT-8 was a beta cell specific antigen.

The initial burden is on the Office to establish a reasonable basis to question the enablement provided for the claimed invention, *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993), MPEP 2164.04. Here, the Examiner has not provided sufficient reasons to doubt the accuracy of the disclosure that ZnT-8 is specific and reliable marker for beta cells and that detection of autoantibodies to ZnT-8 was enabled at the time of invention using the ZnT-8 antigen as disclosed in the specification and conventional detection methods (e.g., immunoassay involving antibody-antigen binding). Moreover, based on the high level of skill in the immunological and medical arts, the Office has not provided reasoning why the detection of autoantibodies to a beta cell specific antigen would not have been useful to one of skill in the art at the time of invention, for example, as an indicator of beta cell destruction or autoimmunity known to associated with type I diabetes.

The Examiner appears to be concerned that the specification does not actually exemplify the claimed method or show that ZnT-8 autoantibodies even exist (OA, page 3, 4th full paragraph). While it is probably true that some subjects may not have detectable autoantibodies to ZnT-8, whether or not a subject has these antibodies is not material, since the specification describes and enables a method for detecting them.

The Examiner did question whether one would have concluded from Examples 2 and 3 that ZnT-8 is specifically expressed by beta cells on the ground that these examples only that ZnT-8 mRNA is present in pancreatic tissue and in beta cells. As noted above, Example 2 and Figs. 1a and 1b show that ZnT-8 mRNA is specifically expressed in beta cells and not in 23 other types of cells, while mRNA encoding the more ubiquitously-expressed actin

protein was identified in all cell types. Moreover, the Applicants have pointed out that the subsequent publications further substantiate the inventors' findings that ZnT-8 is specific and reliable marker for beta cells. Thus, any concern with the accuracy of the disclosure in respect to the specificity of ZnT-8 as a reliable beta cell marker should now be allayed.

The Examiner was also concerned with whether the detection of autoantibodies to ZnT-8, disclosed as a beta cell specific antigen, would have been useful to one of skill in the art. A question posed in the interview was if beta cell destruction was mediated by T cells, then what use would detection of autoantibodies to a beta cell specific antigen like ZnT-8 be.

The present claims do not require that ZnT-8 autoantibodies to mediate beta cell destruction. Rather, the claimed methods are based on the detection of autoantibodies to ZnT-8 so as to provide one of skill in the immunological or medical arts useful information about the status of the subject having autoantibodies to a beta cell specific antigen. Autoantibodies were well-known at the time of invention to be associated with autoimmune diseases such as type I diabetes. Assuming that only cellular mechanisms mediate beta cell destruction and not autoantibodies, one of skill in the art would have understood the significance of autoantibodies to islet-specific proteins as a useful indicator of islet cell destruction which would release and expose the immune system to the detritus of dead beta cells providing degraded, denatured modified self antigens that could initiate autoantibody production. The correlation between autoantibodies to pancreatic antigens and Type 1 diabetes was well-known as of the filing date as shown by *Batstra, et al.*, Clin. Lab. 47:497 (2001), "Prediction and Diagnosis of Type 1 Diabetes Using β-cell Autoantibodies", *Kukreja, et al.*, J. Clin. Endocrinol. Metabol. 84:4371, "Autoimmunity and Diabetes". Other similar publications are referenced and discussed in the prior Declarations of Dr. Favier and Dr. Seve.

Subsequent publications have also shown the significance of ZnT-8 autoantibodies and associated ZnT-8 with autoimmunity. *Wenzlau, et al.*, PNAS 104:17040 (2007) indicates that ZnT-8 is a major autoantigen in human type 1 diabetes and type I diabetes "results from progressive loss of pancreatic islet mass through autoimmunity" (abstract). ZnT-8 "was targeted by autoantibodies in 60-80% of new-onset T1D compared with < 2% of controls" (abstract). *Wenzlau, et al.*, Curr. Opin. Endocrinol. Diabetes Obes. 15:315 states "Initial epitope mapping of ZnT-8 autoantibodies (ZnT8A) in newly diagnosed T1D patients showed that up to 70% of individuals had antibodies reactive to the carboxy terminal 102aa (C-term; aa 268-369) and 10% to the amino terminal 74 aa". These subsequent publications show that one of skill in the art at the time of invention could have used the claimed methods to identify autoantibodies to ZnT-8 disclosed as an islet-cell specific protein. Accordingly, the claimed method was enabled as to how to use as of the date of invention and this rejection cannot be sustained.

Rejection—35 U.S.C. §112, first paragraph

Claims 39, 40 and 46-51 and 55 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. This rejection is moot in view of the amended claim language which deletes "specifically targeting the β cells" and in view of the descriptive support pointed out above for methods of detecting autoantibodies using ZnT-8. Thus, the Applicants respectfully submit that this rejection no longer applies and cannot be sustained.

Rejection—35 U.S.C. §112, first paragraph

Claims 39, 40, 46-51 and 55 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for ZnT-8 fragments. Page 20, lines 9-14 of the specification describe "use of the protein or of the protein fragment as defined above, for. . .the search for autoantibodies directed against the protein according to the invention". The

protein and protein fragments "described above" are ZnT-8 protein (SEQ ID NO: 2) or those fragments of SEQ ID NOS: 7, 8, 9 and 10, see page 19, lines 26-34 and by original claims 24 and 25. Accordingly, this rejection cannot be sustained in view of the amendments to the claims further defining ZnT-8 fragments and in view of this express disclosure.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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